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TITLE: SYNTHESIS OF POTENTIAL PROPHYLACTIC AGENTS AGAINST CYANIDE INTOXICATION

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CONTRACTING ORGANIZATION: Southern Research Institute 2000 Ninth Avenue, South P.O. Box 55305 Birmingham, Alabama 35255-5305

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The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.



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During this report period we prepared examples of all three compound types just described. The 57 new compounds prepared and submitted this period were distributed among these compound classes as follows: sulfur-rich species, 34; polycarbonyl compounds, 14; alkyl- and alkoxy-substituted small nitrogenous heterocycles. 7; and phthalocyanines, 2. Some of these compounds, particularly among the nitrogenous heterocycles, contained ancillary functionality such as carbonyl, which could also neutralize cyanide. In addition to these novel compounds, samples of several materials were re-submitted because of decomposition of the original supply prior to testing, or because additional quantities were required. We have received biological testing data for 41 compounds during this same period, and now have demonstrated activity in three of our four primary target classes (no phthalocyanines have been tested for efficacy at this point). These results are shoping our current synthetic program.

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For the protection of human subjects, the in investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

PI - Signature James R. Piper DATE april 10, 1992

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#### I. INTRODUCTION

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This report documents our efforts during year 2 (9 March 1991 - 8 March 1992) on Contract No. DAMD17-90-C-0011 to identify new and improved prophylactic agents against the toxicity of cyanide. The synthetic effort encompassed the three areas described in the previous annual report, the detailed rationale for which is fully defineated in the original proposal (Southern Research Institute Proposal No. 88-483; USAMRDC Proposal Log No. 88321006); (i) polysulfides and other sulfur-rich compounds which can mediate cyanide detoxification through their interplay with rhodanese and other mammalian sulfur transferase systems; (ii) polycarbonyl-containing compounds which can provide multiple sites for cyanohydrin formation, one of the key detoxification routes of pyruvate and related compounds; and (iii) heteroaromatic compounds capable of undergoing cyanation, thereby removing cyanide. We also report our initial investigation into a novel class of promising prophylactic substances, phthalocyanines and porphyrins, which can sequester cyanide through complexation with the constituent metal ion.

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This report compiles the synthetic procedures described in reports submitted for quarters 5-8 of this contract. We have also colligated structures of all compounds supplied for testing with their corresponding identification numbers and, where available, biological test data. Experimental procedures are provided following each section outlining the syntheses.

The following instrumentation methods and procedures were used. All solvents and materials were reagent grade and were either used as received or purified as required. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra wore run with a Nicolet NMC NT300 NB spectrometer operating at 300.65 Mhz with tetramethylsilane as an internal reference. Chemical shifts ( $\delta$ ) for multiplets were measured from the appropriate centers. The mass spectral data were obtained from a Varian MAT 311A mass spectrometer in fast atom bombardinent (FAB) or electron-impact (EI) mode (direct probe temperature 20 °C), as indicated. Infrared data were obtained with a Nicolet 10-MX spectrometer. In most cases, only strong or medium peaks in the 1800-600 cm<sup>-1</sup> range were reported. UV absorption spectra were determined in the appropriate solutions (pH 1 (0.1 N HC1), pH 7 buffer, and pH 13 (0.1 N NaOH)) with either a Cary 17 spectrometer or a Perkin-Elmer Model Lambda 9 UV/VIS/NIR spectrophotometer. Melting point data was obtained with a Mel-Temp Capillary Melting Point apparatus, and all melting points are uncorrected. Elemental analysis data were obtained from either an inhouse Perkin Elmer Model 240 Elemental Analyzer or from Atlantic Microlab of Atlanta, Georgia.

## II. NITROGENOUS AROMATIC HETRROCYCLES.

## A. N-Alkoxy Qustersary Salts.

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During this report period we prepared two new N-alkoxy quasernary saits which can form covalent adducts with cyanide.<sup>1-3</sup> The synthesis of these compounds was prompted by the activity data reported for a previously submitted derivative, SRI 7726 (BM 07230). The structures of these compounds are shown below (1 and 2); both were prepared by alkylation of the appropriate commercially available N-oxides following standard procedures as reported earlier. Table 1 summarizes the physical properties of these new compounds.

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### B. N-Alkyl Quaternary Salts.

The five N-alkyl quaternary heterocyclic salts that were submitted this period are depicted below (3-7). These compounds were prepared because of literature reports that pyridinium salts with glycosyl substituents at the 1-position and electron withdrawing groups at the 3-position react rapidly to form stable cyano adducts.<sup>4,5</sup> Glycosyl bromides were prepared by reported procedures,<sup>6</sup> then coupled with the parent heterocyclic compound. The results and physical properties of these agents are presented in Table 1.



TABLE 1. QUATERNARY NITROGENOUS HETEROCYCLES.

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cation, anion Mass (FAB) 452, 79 453, 79 289, 79 275, 79 460, 79 380, 79 195, 7.87 12.14 7.15 2.66 2.66 2.59 2.61 5.25 3.24 Elemental Analyses Ş Calcd Found 6.23 6.29 5.66 6.55 6.50 4.92 4.85 5.02 4.72 4.73 4.87 Ŧ 37.10 36.96 51.12 50.90 37.13 47.38 45.10 45.00 46.94 52.06 46.97 ¥ Molecular Formula (Formula Mt.) C12H22Bn2M20.H20 (388.16) CzyHzBrN2010 (533.34) C1,HyBn2N,0 (356.12) C2,H3,BrN0,0 (532.35) C10H3C1M.02 (230.70) C24H, BrN0, (540.37) C(\$H23BrN0 (\$60.28) 195-200 (111.° mp 195-200) 184-185 (lit.<sup>\*</sup> mp 182-190) 158-159 (111.<sup>b</sup> =p 158-159) ()1t.<sup>4</sup> mp 142-143) (lit. mp 175-176) M.P., °C 182-184 58-60 175 Yield, X 39 63 3 52 3 3 5 Structure No. N

\*Augustinssan, K. B.; Hasselquist, H., Acta Chemica Scand. 1961, 15, B17. "Lovesey, A. C., J. Ned. Chem. 1970, J3, 693. "Haynes, L. J.; Todd, A. R., J. Chem. Soc. 1950, 303. "Lovesey, A. C.; Ross, W. C. J., J. Chem. Soc. (B) 1969, 192.

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### EXPERIMENTAL SECTION FOR PART II.

#### Systhesis of N-{2-trimethylammonlum)sthery}-2,6-dimethylpyridisium Dibromids.<sup>19</sup>

A mixture of 2-bromosthyltrimethylammonium bromide (8.2 mmol), 2,6-lutidine-N-oxide (8.1 mmol), and 5 mL of water was heated in a flask at 100 °C for 56 h. The unreacted bromosthyl compound was removed by adding an additional portion of water (10 mL), followed by evaporation under reduced pressure. This process was repeated twice. The lutidize which was formed during the reaction was removed by extraction with chloroform. The remaining product was treated with ethanol, filtered, and the residue dissolved in boiling ethanol. The solution was treated with activated carboa, filtered, and the filtrate cooled to get the crystalline compound. The product was dried over  $P_2O_5$  under reduced pressure. Yield 68%; m.p. 175 °C (Lit 175-5). Analysis for  $C_{12}H_{23}ON_2Br_2H_2O$ . Calculated: C, 37.13; H, 6.23; N, 7.22. Found: C, 37.14; H, 6.29; N, 7.15. Mast spec. 289, cation, 79 anion.

Synthesis of N-(2-(irimetic glammonium)) ethoxy]4-methylpyridinlum dibromide.<sup>10</sup> A mixture of 2bromoethyltrimethylammonium i romide (14 mmol) and 4-methylpyridine-N-oxide (32 mmol) was refluxed in acetonitrile (10 mL) on a watter bath for 10 h. The 2-bromoethyltrimethylammonium bromide slowly dissolved and a light brown solid separated, which was filtered and washed with acetonitrile (20 mL) and then acetone, and crystallized for -a-butanol, followed by drying under reduced pressure. Yield 61%; m.p. 184-185 °C (Lit 182-190 °C). A systs for C<sub>11</sub>H<sub>20</sub>ON<sub>2</sub>Br<sub>2</sub>.

Acetobromo-D-glucopyraness used to prepare 3-5 and acetobrome-D-ribufuraness used to prepare 6 were prepared by the procedure of Haynes and Todd without modification.<sup>6</sup>. Chloromethyl propyl ether used to prepare 7 was prepared by the procedure of Henze et al.<sup>11</sup>

1,3-Disubstituted pyridinium halides 3, 5-7 and the isequinelinian breakle 4 were prepared by treating the parent heterocyclic compound with the appropriate bromide or with chloromethyl propyl ether in refluxing acetonitrile using the general procedure of Lowsey.<sup>5,13</sup> Products crystallized from the reaction solutions. Names of the compounds are as follows: 3-acetyl-1-(2,3,4,6-tetraacetyl- $\beta$ -D-glucopyranosyl)-pyridinium bromide (3); 1-(2,3,4,6-tetraacetyl- $\beta$ -D-glucopyranosyl)isoquinolinium bromide (4); 3-amino-carbonyl-1-(2,3,4,6-tetraacetyl-D-glucopyranosyl)-pyridinium bromide (5); 3-acetyl-1-(2,3,5-triacetyl- $\beta$ -D-ribofuranosyl)pyridinium bromide (6); and 3-aminocarbonyl-1-(propoxymethyl)pyridinium chloride (7).

A. Derivatives of 4-Phenyl-2,4-dioxebutyric Acid.

Our rationale for preparing polycarbonyl compounds as cyanide ion traps is based upon the stability and facile formation of cyanohydrin adducts. During the past year we have continued our exploration of substituted phenylbutyrates resulting from the condensation of the corresponding substituted acetophenone with diethyloxalate.<sup>7,8</sup> The structures of the six additional examples of this class that were submitted for screening this period are illustrated below. The carboxylate 5 was prepared by hydrolysis of the ethyl ester, a compound that was described and submitted last year. The physical properties of these compounds are summarized in Table 2.

$$\begin{array}{cccccc}
& & & & & \\ & & & & \\ & & & & \\ &$$

## B. Derivatives of 3-Phenyl-2-oxopropionic Acid.

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As a second class of carbonyl-containing compound capable of cymide detoxification, we chose to prepare the series of substituted phenylpyruvates shown below. The synthesis of these substances was based upon literature methods, beginning with a substituted benzaldehyde (Eq. I). Thus, the starting aldehyde was condensed with N-acetylglycine, and the resulting oxazolinone (A) treated with acid to cleave the ring, yielding the desired pyruvic acid derivative. Table 3 summarizes the data obtained for these compounds.



## EXPERIMENTAL SECTION FOR PART III.

#### General Procedure for the Preparation of Substituted-phenyl-2,4-dioxobutyrate Esters.

Freshly cut Na (1.2 g, 0.0521 g-atom) was added to EtOH (100-mL) under N<sub>g</sub> in a 500-ml, 3-neck flask equipped with a mechanical stirrer, a ground glass stopper, and a gas inlet tube. The mixture was stirred until the Na had completely dissolved, then equimolar amounts (0.05 mole each) of diethyl oxalate and the appropriate acetophenone were added. The reaction mixture was stirred for 3 h, resulting in the formation of a thick slurry. If the thickness of the slurry interfered with stirring, more EtOH was added. The slurry was suction filtered and washed with anhydrous EtOH until the wash solvent was coloriess and the salt relatively dry. The salt was then added to H<sub>2</sub>O, and the resulting suspension was acidified to pH 5 by the dropwise addition of glacial AcOH with stirring. The resulting lighter-colored solid was filtered and dried *in vacuo*. When required, the compounds were further purified by adding to H<sub>2</sub>O, reacidifying with AcOH to pH 3, and drying *in vacuo*.

11

Ethyl 4-(3-fluorophenyl)-2,4-dioxobutyrate. Mp 56-57 °C; MS (FAB) m/e 239 (M + 1); IR (KBr) 3098.8, 2995.6, 1742.8, 1621.4, 1609.3, 1579.4, 1447.6, 1269.3, 1258.4, 1181.6, 1137.4, 1024.1, 774.3 cm<sup>-1, 1</sup> HNMR (Me<sub>2</sub>SO-d<sub>8</sub>) & 14.60 (br s, 1, H-4), 7.94 (d, 1, H-6), 7.87 (d, 1, H-5), 7.63 (m, 1, H-2), 7.58 (m, 1, H-4), 7.13 (s, 1, H-3), 4.32 (q, 2,  $-OCH_2CH_3$ ), 1.33 (t, 3,  $-OCH_3CH_3$ ), also very weak multiplets at 4.61, 4.21, 1.26 for the unenolized tautomer. Anal. Calcd. for C<sub>13</sub>H<sub>11</sub>O<sub>4</sub>: C, 60.50; H, 4.62. Found: C, 60.56; H, 4.69.

Ethyl 4-(3-methoxyphenyl)-2,4-dioxobutyrzte. Mp 53-54 °C; MS (FAB) m/e 251 (M + 1); IR (KBr) 3132.4, 3089.9, 3000.0, 2845.6, 1742.4, 1595.6, 1580.0, 1470.0, 1185.2, 1135.6, 1021.4, 772.9, cm<sup>-1</sup>; <sup>1</sup> HNMR (Me<sub>3</sub>SO-d<sub>8</sub>)  $\delta$  14.70 (br s, 1, H-4), 7.65 (d, 1, H-6'), 7.51 (s, 1, H-2'), 7.48 (d, 1, H-5'), 7.27 (m, 1, H-4'), 7.08 (br s, 1, H-3), 4.32 (q, 2, -*OCH*<sub>3</sub>CH<sub>3</sub>), 3.85 (s, 3, -OCH<sub>3</sub>), 1.33 (t, 3, -OCH<sub>3</sub>CH<sub>3</sub>), also very weak multiplet at 4.60 for the uzenolized tautomer. *Anal.* Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>5</sub>: C, 62. 40; H, 5.60. Found: C, 62.34; H, 5.78.

Ethyl 4-(3-chlorophenyl)-2,4-diexobutyrate. Mp 55-57 °C; MS (FAB) m/e 255 (M+1); IR (KBr) 3120.9, 3100.0, 3016.6, 2999.8, 2950.1, 2917.6, 1975.0, 1732.4, 1626.9, 1607.9, 1594.8, 1560.7, 1363.7, 1276.8, 1271.6, 1267.0, 1223.9, 769.2 cm<sup>-1</sup>; <sup>1</sup> HNMR (Me<sub>3</sub>SO-d<sub>6</sub>)  $\delta$  14.30 (br s, 1, H-4), 8.06 (s, 1, H-2), 8.02 (d, 1, H-6), 7.76 (m, 1, H-4), 7.60 (t, i, H-5), 7.09 (br s, 1, H-3), 4.32 (q, 2, -OCH<sub>3</sub>CH<sub>3</sub>), 1.33 (t, 3, -OCH<sub>3</sub>CH<sub>3</sub>), also very weak multiplets at 4.62, 4.19, 1.22 for the unenolized tautomer. And. Calcd. for C<sub>12</sub>H<sub>11</sub>ClO<sub>4</sub>: C, 56.69; H, 4.33. Found: C, 56.56; H, 4.30.

Ethyl 4-(3-altrophanyl)-2,4-diaxabetyrata. Mp 73-74 °C; MS (FAB) m/x 266 (M + 1); IR (KBr) 3073.9, 2993.5, 1735.7, 1614.0, 1604.0, 1530.3, 1477.2, 1366.0, 1349.8, 1272.3, 1130.7, 1072.6, 1019.2, 781.5, 714.1, 673.4 cm<sup>-1</sup>; <sup>1</sup> HNMR (Ma<sub>2</sub>SO-d<sub>4</sub>) § 8.71 (a, 1, H-2'), 8.51 (m, 1, H-6'), 8.51 (m, 1, H-4'), 7.87 (t, 1, H-5'), 7.18 (br s, 1, H-3), 4.35 (a, 2,  $-OCH_2CH_2$ ), 1.33 (t, 3,  $-OCH_2CH_2$ ), also very week multiplets at 4.73, 4.25, 1.25 for the unebolized mutomer. Anal. Calcd. for  $C_{12}H_{11}NO_6$ ; C, 54.34; H, 4.15; N, 5.28. Found: C, 54.26; H, 4,16; N, 5.14.

Ethyl 4-(3-methylphenyl)-2,4-dioxobutyrate. Mp 37-39 °C; MS (FAB) m/e 235 (M + 1); I% (KBr) 2987.5, 1976.2, 1729.1, 1627.3, 1597.9, 1591.2, 1579.2, 1518.2, 1511.5, 1470.9, 1444.2, 1364.8, 1270.7, 1257.7, 1175.5, 1115.6, 1108.2, 1085.5, 1029.0, 867.9, 770.2, 628.1 cm<sup>-1</sup>, <sup>1</sup> HNMR (Me<sub>3</sub>SO-d<sub>6</sub>) § 7.82 (br s, 1, H-2), 7.80 (d, 1, H-6), 7.45 (m, 1, H-5), 7.45 (m, 1, H-4), 4.40 (br s, 2, H-3), 4.27 (q, 2,  $-OCH_{3}CH_{3}$ ), 2.19 (s, 3,  $CH_{3}$ -3p), 1.29 (t, 3,  $-OCH_{3}CH_{3}$ ), also very weak multiplet at 6.90 for the unenolized tautomer. Anal. Calcd. for C<sub>13</sub>H<sub>14</sub>O<sub>4</sub>: C, 66.67; H, 5.98. Found: C, 66.70; H, 6.04.

## Syntaesis of Substituted Phenyl Pyruvates (3-Phenyl-2-oxopropionates).

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A solution of N-acetylglycine (7.0 g, 60 mmol) in 20 mL acetic acid and 21 mL acetic anhydride containing sodium acetate (14.4 g, 176 mmol) and 64 mmol of a substituted benzaldehyde was stirred at 100 <sup>\*</sup>C for 2 hrs. After the solution was cooled to 10<sup>\*</sup>C, 100 mL H<sub>2</sub>O was added with vigorous stirring. The resulting precipitate (A) was collected by filtration.

A solution of A in 150 mL HOAc was heated to 100 °C. Five mL  $H_3O$  was added and the solution stirred at 100 °C for 15 min. Upon allowing the solution to cool slowly to room temperature, a precipitate formed (B). In some cases, no precipitate formed; the solution was then stripped to dryness to obtain B.

A suspension of B in 150 mL 3N HCl stirred at reflux for 7 hrs. After the mixture was cooled to 0  $^{\circ}$ C, the product C was collered by filtration and washed with cold H<sub>2</sub>O and dried under vacuum.

(4-Nitrophenyi) pyravic acid (exists primarily in enolized form).

M.p. 182-184 °C; MS (neg. fab) m/e 208 (M - 1); IR (KBr) 3475.7, 3473.2, 3075.0, 1975.0, 1765.0, 1681.4, 1591.7, 1512.5, 1446.6, 1324.6, 1316.4, 1244.4, 1205.1, 875.36, 862.92 cm<sup>-1</sup>; <sup>1</sup>H NMR (Me<sub>3</sub>SO-d<sub>8</sub>) 6 13.60 (br s, 1H, H<sup>+</sup>) 10.26 (br s, 1H, H<sup>+</sup>), 8.19 (n, 2H, H-3'), 7.98 (m, 2H, H-2'), 6.54 (s, 1H, H-3). There was also a small signal (1/14 the intensity of the peak at 6.54) at 4.38 for the unenolized tautomer. *Anal.* calcd for C<sub>6</sub>H<sub>7</sub>NO<sub>5</sub>: C, 51.67; H, 3.35; N, 6.70. Found: C, 51.84; H, 3.32; N, 6.55.

(4-Bromophenyl)pyruvic acid (exists primarily in enolized form).

Mp 177-185 °C; MS (seg FAB) m/e 242 (M - 1); IR (KBr) 3467.8, 3465.8, 1905.9, 1685.4, 1649.5, 1444.0, 1219.7, 1200.0, 1074.9 cm<sup>-1</sup>; <sup>1</sup>H NMR (Me<sub>2</sub>SO-d<sub>2</sub>) 6 13.26 (br s, 1H, H<sup>+</sup>), 9.48 (br s, 1H, H<sup>+</sup>), 7.71 (m, 2H, H-3'), 7.53 (m, 2H, H-2'), 6.37 (s, 1H, H-3). There was a small signal (1/14 the intensity of the peak at 6.37) at 4.15 for the unenolized tautomer. Anal. calcd for C<sub>2</sub>H<sub>7</sub>BeO<sub>2</sub>: C, 44.44; H, 2.88. Found C, 44.49; H, 2.87.

(4-Chlorophenyl)pyravic acid (exists primarily enolized form).

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Mp 183-187 °C; MS (neg FAB) m/e 197 (M - 1); IR (KBr) 3465.9, 1911.3, 1679.8, 1664.2, 1436.1, 1409.5, 1225.2, 1201.5, 1088.7, 867.55, 821.10 cm<sup>-1</sup>; <sup>1</sup>H NMR (Me<sub>2</sub>SO-d<sub>6</sub>) 6 13.31 (br s , 1H, H<sup>+</sup>), 9.47 (br s, 1H, H<sup>+</sup>), 7.78 (m, 2H, H-3), 7.40 (m, 2H, H-2'), 6.39 (s, 1H, H-3). There was a small signal (1/14 the intensity of the peak at 6.39) at 4.18 for the unenolized tautomer. Anal. calcd for C<sub>6</sub>H<sub>7</sub>ClO<sub>3</sub>: C, 54.41; H, 3.53. Found: C, 54.08; H, 3.43.

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Structure No.

TABLE 2. 4-PHENYL-2,4-DIOXOBUTYRATES.								
Yieid, %	M.p., *C	Molecular Formula (Formula WL)	Elen %C	Calco Found %H	asiyes I I 96N			
75	110-113	C <sub>13</sub> H <sub>11</sub> NO <sub>8</sub> (265.22)	54.34 54.22	4.15 4.34	5.28 5.42			

8	75	110-113	C <sub>12</sub> H <sub>11</sub> NC <sub>8</sub> (265.22)	54.34 54.22	4.15 4.34	5.28 5.42
9	69	<b>56-</b> 57	C <sub>12</sub> H <sub>11</sub> O <sub>4</sub> (238.21)	60.50 60.56	4.62 4. <del>69</del>	
10	58	53-54	C <sub>12</sub> H <sub>14</sub> O <sub>6</sub> (250.25)	62.40 62.34	5.60 5.78	
11	69	55-57	C <sub>13</sub> H <sub>11</sub> ClO <sub>4</sub> (254.74)	56.69 56.56	4.33 4.30	
12	35	37-39	C <sub>12</sub> H <sub>14</sub> O <sub>4</sub> (234.25)	<b>66.67</b> 66.70	5.98 6.04	
13	\$3	73-74	C <sub>12</sub> H <sub>11</sub> NO <sub>6</sub> (265.22)	54.34 54.26	4.15 4.16	5.28 5.14

	TABLE 3. 3-PHENYL-2-OXOPROPIONATES.							
Structure No.	icture No. Yield, % M.p., °C (Formula (Formula )				smental Analyses Calcd Found %H %N			
14	89	182-184	C <sub>9</sub> H <sub>7</sub> NO <sub>8</sub> (209.157)	51.67	3.35 6.70			
15	12	177-185	C <sub>6</sub> H <sub>7</sub> BrO <sub>3</sub> (243.06)	4.44 44,49	2.88 2.87			
16	94	183-187	C <sub>9</sub> H <sub>7</sub> C1O <sub>3</sub> (198.61)	54.41 54.08	3.53 3.43			
17	66	151-156	L <sub>8</sub> H <sub>7</sub> FO <sub>3</sub> (182.15)	59.34 59.46	3.85 3.88			
18	60	141-145	C <sub>9</sub> H <sub>6</sub> O <sub>5</sub> (164.16)	65.85 66.02	4.88 5.07			
19	Purchased from Aldrich	204-205	C <sub>9</sub> H <sub>9</sub> O <sub>4</sub> (180.16)	60.00 50.00	4,44 4,45			
20	66	175-182	C <sub>11</sub> H <sub>12</sub> O <sub>5</sub> (224.21)	58.93 58.91	5.36 5.42			
21	81	180-185	C <sub>10</sub> H <sub>10</sub> O <sub>4</sub> (194.19)	61.85 61.90	5.19 5.27			

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#### IV. METAL COMPLEXES

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As discussed in detail in Quarterly Report 7, we have embarked upon a synthetic program to explore the utility of porphyrins and phthalocyanines for cyanide antagonism. Briefly, our promise for this approach is that the toxicity of metal ions, which have a high affinity for cyanide and effectively sequester it *in vitre*, can be reduced sufficiently if suitable water soluble complexes can be prepared. Thus, simple EDTA complexes of cobalt are already employed as cyanide antidotes in several countries, reinforcing our belief that further investigation of this concept is warranted. This report period, the two phthalocyanime complexes depicted below were prepared and submitted for screening; several additional examples are in various stages of preparation and will be submitted shortly.



### **EXPERIMENTAL SECTION FOR PART IV.**

### Synthesis of Fo(II) Suifothalocyanine.13

The monosodium salt of 4-sulfophthalic acid (0.04 m), ammonium chloride (.023 m), ures (0.25 m), ammonium molybdate (.0002 m), and iron sulfate (.012 m) were ground together. Nitrobeanene (10 mL) was heated to 180 °C in a three neck flask fitted with condenser and thermometer. The solid mixture was added slowly with stirring while keeping the temperature between 160-190 °C. The heterogeneous mixture was heated 6 h at 180 °C. The crude product, a solid cake, was grounded and washed with methanol until the nitrobenzene filtrate was no longer discolored. The remaining solid was added to 275 mL of 1N HCl saturated with sodium chloride. The solution and accompanying undissolved material were briefly heated to boiling, cooled to room temperature, and filtered. The resulting solid was dissolved in 200 mL of 0.1 N NeOH. The solution was heated to 20 °C and insoluble impurities were immediately separated by filtration. Sodium

chloride (135 g) was added to the solution. At this point some of the solid product precipitated. The sturry was again heated and stirred at 50 °C until ammonia evolution stopped. The product was obtained by filtration. The solid was washed with 30% aquecus alcohol until the filtrate was chloride free. The product was refluxed for 5 h in 100 mL of absolute alcohol. The pure product was obtained, filtered, and dried overnight *in vacuo* over  $P_3O_3$ .

Analysis: Mass spec M<sup>-</sup>, 977, M - Na, 955; M - 2Na, 933, M - 3Na, 911, M - 4Na, 888. Calculated for: C<sub>32</sub>H<sub>18</sub>N<sub>8</sub>O<sub>19</sub>S<sub>4</sub>Na<sub>4</sub>Fe.3H<sub>2</sub>O (FW 1032.6). C, 37.20; H, 1.95; N, 10.85. Found: C, 36.2; H, 1.95; N, 11.00.

Synthesis of Cobalt Sulfophthalecyasine.<sup>13</sup> The monomodium salt of 4-sulfophthalic acid (0.04 mol), ammonium chloride (0.23 mol), uree (0.25 mol), ammonium molybdate (0.0002 mol), and cobalt sulfate (0.12 mol) were ground together and heated to 120-140 °C for 30 min; subsequently, the temperature was raised to 180-200 °C for 4 h. The resulting residue was powdered and then added to a naturated solution of NaCl in 1N HCl (300 mL). This solution was beated to 70 °C, cooled to room temperature, and filtered. The residue was dissolved in 0.1N NaOH solution (250 mL), heated to 80 °C and filtered quickly. NaCl (125 g) was added to the filtrate, which was reheated to 80 °C for 2 h. The product precipitated after cooling, and was filtered, washed with 80% ethanol until chloride free, then refluxed for 4 h in absolute alcohol (50 mL). After another filtration the product was dried under reduced pressure over  $P_2O_5$ . Yield 72%. Analysis for  $C_{32}H_{13}N_8O_{12}S_4Na_4Co-2H_2O$  (FW 1015.67). Calculated: C, 37.82; H, 1.59; N, 11.03. Found: C, 37.14; H, 1.69; N, 11.43.

### V. SULFUR-CONTAINING COMPOUNDS

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## A. Disuifides and Related Compounds.

Continuing work reported in the Annual Report for year 1, the following two disulfides (24, 25) were prepared according to methods shown in the accompanying scheme and submitted for testing this period. Both compounds were already known from the patent literature. Physical data is reported in Table 4.



## 2. Thieralfanates.

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The primary thrust of our efforts this report period has involved synthesis and purification of thiosulfonate and thiosulfate species which, as already mentioned, act to detoxify cynnise through interaction with the mammalian sulfurtransferase pathway. In particular, these compounds act as substrates in rhodanese-promoted reactions.<sup>6</sup> In the thiosulfonate group, we have subsaided ten novel agents designed for this purpose, whose structures are given below.



These compounds were prepared by treatment of the corresponding sulfony! chlorides with sodium sulfide as described in the literature.<sup>9</sup> In addition to the submitted compounds, several thiosulfonesses were prepared as intractable mixtures which could not be purified. Table 5 summarizes the properties of the submitted thiosulfoness.

#### C. Thiosalfates.

The first thiosulfanss prepared in this program were zwitterionic araino-substituted derivatives, formed by treatment of the corresponding bromoalkylamine with magnetium thiosulfate. In addition, S-sulfo derivatives of cysteine and penicillamine were synthesized by treatment of the parent thiol with chlorosulfonic acid. The barium salt of S-sulfoglutathione warstmilarty prepared, and after purification was converted to the sodium salt for efficacy testing. The structures of these sulfane sulfur donors, and of additional examples subsequently submitted, are summarized in the diagrams below, and their physical data follow in Table 6.

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## D. 3-H-1,2-Dithiole-3-thioses.

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Two routes were investigated for the preparation of the title compounds (Equ. II, III). The first method consistently produced reduced yields relative to method III, so the latter preparation is now being employed. So far a single example of this series (structure 57, Eqn. III) has been submitted, although preparation of additional examples is in progress. Date for this compound is summarized in Table 7.



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Synthesis of 5,5-Bis(thiemethyi)hydantoin (24) in Three Steps. Step 1. 1,3-Bis-(bennyithie)acetone. Na metal (23.0 g, 1.00 g-atom) was added in small pieces to a well-stirred solution of benavyl mercaptan (118 mL, 1 mol) in 400 mL absolute ethanol, which was cooled in an ice bath during the addition of Na. A solution of 1,3-dichloroacetone (63.5 g, 0.5 mol) in 100 mL absolute ethanol was added dropwise during a 2 h period with continued stirring and cooling. After the addition was completed, the reaction was allowed to stir at 20-25 °C overnight (18 h). The solvent was evaporated in vacuo, and the residue was taken up in 400 mL other and filtered from inorganic matter. The filtrate was washed twice with 100-mL portions of H<sub>2</sub>O, dried over MgSO4, then evaporated in vacuo to a dark viscous oil (104.7 g). Step 2. 5,5-Bis(beaxylthlomethyl)hydaateln. The residue from Step 1 in 1050 mL absolute ethanol was warmed to 60-70 °C with stirring in an oil bath. A solution of potassium cyanide (35 g) in 350 mL H<sub>2</sub>O was added followed by 210 g of solid ammonium carbonate. Stirring was continued at 60-70 °C for 24 h. Upon cooling a brown solid separated and was collected by filtration, then washed with ethanol and HaO to give 77 g of light beige solid. Step 3. 5.5 Bis(thiomethyl)hydantein (24). A portion (4.0 g) of the solid from Step 2 was dissolved in 100 mL of liquid NHs. The solution was treated with small portions of Na with vigorous stirring antil the mixture developed permanent blue color. The blue color was discharged by the addition of ammonium chloride, then more ammonium chloride was added (a quantity equivalent to the Na used). The ammonia was allowed to evaporate at 20-25 °C overnight under a slow stream of N, leaving a solid residue. Column chromatography (using 60-200 mesh silica gel and elution with CHCl<sub>3</sub>-MeOH, 95:5) was used to obtain sure 24, mp, 198-202 \*C. Anal. Caled for CoHeN2O252; C, 31.25; H, 4.17; N, 14.58. Found: C, 31.10; H, 4.02; N, 14.40. Mass. m/z 92, M<sup>+</sup>. <sup>1</sup>H NMR (Me<sub>2</sub>SO-d<sub>a</sub>) 6 10.84 (br s, 1, NH-3), 7.78 (s, 1, NH-1), 2.80 (d, 2, J = 14, CH<sub>2</sub>SH),  $2.71 (d, 2, J = 14, CH_{2}SH), 2.36 (br s, 2, SH).$ 

4-Amino-1,2-diothiolane-4-carbexylic Acid (25) in Three Steps from 5,5-Bis(benzylthiomethyl)hydantoin. Step 1. 2,2-Bis(benzylthiomethyl)glyclae. Crude 5,5-bis(benzyl-thiomethyl)hydantoin (70 g) (see under synthesis of 24) in 1.75 L of H<sub>3</sub>O containing 215 g of dried Ba(OH)<sub>3</sub> was refluxed for 12 days. The reaction mixture was cooled and made strongly acidic with concentrated hydrochloric acid to dissolve suspended barium suits. The undissolved solid was collected by filtration and washed with H<sub>3</sub>O. The solid was then added to ethanol and the mixture was stirred 20 min. before the insoluble was collected giving 43.42 g of product. Step 2. 2,2-Bis(thiomethyl)glyclae. A solution of 41.25 g (119 mmolas) of the product from

Step 1 in 910 mL anhydrous NH<sub>3</sub> was treated with Na metal in small pieces with vigorous stirring until the mixture developed a permanent blue color. The blue color was discharged by the addition of a small amount of ammonium chloride. More ammonium chloride, equivalent to the quantity of Na used, was then added. The ammonium chloride. More ammonium chloride, equivalent to the quantity of Na used, was then added. The ammonium chloride. More ammonium chloride, equivalent to the quantity of Na used, was then added. The ammonium chloride. More ammonium chloride, equivalent to the quantity of Na used, was then added. The ammonium chloride, and the exposet at 20-25 °C overnight under a slow stream of N<sub>2</sub>. The residue was taken up in 800 mL H<sub>2</sub>O, and the pH of the solution was adjusted to 6 by the addition of dilute HCl. The solution was then extracted with 300 mL Et<sub>2</sub>O. The ethereal phase was discarded, and the aqueous phase containing the product was used in Step 3 which follows. Step 3. 4-Amine-1,2-dithielane-4-carbexylic Acid (25). The aqueous phase from Step 2 was added slowly to stirred 2N I<sub>3</sub>-KI solution. The excess was destroyed with aqueous 10% NaHSO<sub>2</sub>. The solution was extracted with 300 mL Et<sub>2</sub>O, and the aqueous phase was neutralized with concentrated NH<sub>4</sub>OH. The neutral solution was filtered free of undissolved material, and the filtrate was concentrated in vacuo to 500 mL. A yellow solid separated out and was filtered off, then washed with H<sub>2</sub>O to give 25 as a monohydrate, mp 165-173 °C dec. Anal. Calcd for C<sub>4</sub>H<sub>7</sub>NO<sub>2</sub>S-H<sub>2</sub>O: C, 26.23; H, 4.92; N, 7.65. Found: C, 26.24; H, 4.90; N, 7.79. Mass, m/z 183, M+. <sup>1</sup>H NMR (Me<sub>2</sub>SO-d<sub>6</sub>) 6 7.88 (br s, 1, NH<sub>2</sub>), 3.50 and 3.32 (two d, 4, due to nonequivalent CH<sub>2</sub> groups).

Sodium Methanesulfonothioate (26) and analogous compounds 27-35 were propared by a reported general procedure<sup>9</sup>. The procedure for the preparation of 29 is given as a typical example. Benzenesulfonyl chloride (10 g, 57 mmol) was added dropwise to a stirred solution of Na<sub>3</sub>S-9H<sub>3</sub>O (13.6 g, 57 mmol) in H<sub>3</sub>O (50 mL) kept at 95-100 °C. The stirred mixture was then refluxed overnight (about 16 h). The resulting clear solution was evaporated to dryness (1 mm, rotary evaporator, bath 20-25 °C). The dry residue was extracted with hot EtOH and was recrystallized twice from EtOH.

Disodium  $S_{2}^{-1}$ , 2-Ethanediyi Bis(thiesulfate) (36) and Homologs 37-40. The  $\alpha_{1}\omega$ -dibromonikane and two molar equivalents of Na<sub>3</sub>S<sub>3</sub>O<sub>3</sub>-3H<sub>3</sub>O were dissolved in EtOH-H<sub>3</sub>O (1:1 by volume, 50 mL per 4.0 mmole of Na<sub>3</sub>S<sub>3</sub>O<sub>3</sub>-H<sub>3</sub>O). The solution was refluxed 2 h, cooled, and evaporated to drymens. The radius was recrystallized from EtOH (9:1 by volume).

Sodium S-[4-(Methexycarbonyl)butyl] Thiosulfate (41) and Sodium S-(7-Carboxyhoptyl) Thiosulfate (42). Equimolar amounts of the appropriate  $\omega$ -substituted brome compounds and Na<sub>3</sub>S<sub>2</sub>G<sub>3</sub>-SH<sub>3</sub>O in H<sub>2</sub>O containing sufficient EtOH to produce a clear solution was refluxed 2 h, cooled, and evaporated *in pacue*. The residues were recrystallized from H<sub>3</sub>O by addition of EtOH three or four times or until the precipitated solid was free of NaBr. Products were dried *in vacue*.

#### Synthesis of Rifenctional Bunte Saits (43, 44).

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A mixture of dichloroscetone or  $\alpha_1\alpha'$ -dibromo-O-xylene (0.1 m) and sodium thiosulfate (0.2 m) in 50% alcohol (60 mL) was reflaxed for 10 min - 2 hr. Solvent was removed to dryness and 90% alcohol added, followed by warming to 50 °C. On cooling the product separated and after filtration was crystallized 3-4 times from hot aqueous ethanol (90%).

Thiosulfaric scid, 2 exe-S.S-1,3-propanedlyl ester, disediam sait (43). Yield 62%; mp 138-40 °C. Anal. calcd for C<sub>2</sub>H<sub>4</sub>O<sub>7</sub>S<sub>4</sub>Ns<sub>2</sub>1H<sub>2</sub>O: C, 10.46; H, 1.75. Found C, 10.34; H, 1.69. Mass spec. (M - Na) 303.

Thiosulfuric acid, S.S'-(O-phenylene)diplester, disedium salt (44). Yield 39%, mp, 195-198 °C. Anal. calcd for C<sub>8</sub>H<sub>8</sub>O<sub>6</sub>S<sub>4</sub>Na<sub>2</sub>1.5H<sub>2</sub>O: C, 23.94; H, 2.76. Found: C, 24.05; H, 2.63. Mass spec (M - Na)<sup>-</sup> 351, (M + Na)<sup>+</sup> 397.

S-(2-Aminoethyl)-Thiomifuric Acid (45) and S-(3-Aminopropyl)-Thiomifuric Acid (47). A solution of equimolar amounts of 2-bromoethylamine hydrobromide (for 6) or 3-bromopropylamine hydrobromide (for 7) with  $MgS_2O_3$ -6H<sub>2</sub>O in MeOH (1 mL per mmol of  $MgS_2O_3$ -6H<sub>2</sub>O) was kept at 60 °C for 1 h. The cooled solution deposited the product 6 or 7. Results are included in Table 2.

#### Synthesis of 2-Dimethylaminoethanethiosulfuric Acid (46).

A mixture of 2-dimethylaminoethylchloride hydrochloride and magnesium thiosulfate (0.1 m) in methanol (2.5 mL) was heated on a water bath at 60-65 °C for 2 h. Methanol was then removed under reduced pressure, leaving a viscous product. Aqueous ethanol (95%) was added to precipitate the solid product, which was recrystallized from 95% ethanol 3-4 times until MgCl<sub>2</sub> free. Yield 42%, mp 160-162 °C. Anal. calcd for: C, 24.96; H, 6.17; N, 7.27. Found: C, 25.0, H, 6.17; N, 7.03. Mass spec. (M - H)<sup>-</sup> 184.

S-Suifocysteine (48), S-Suifopenicillamine, and S-Suifopenicillamine (49), and S-4-Aminophenyi Thiesulfuric Acid (50). These three candidates were prepared by treatment of the corresponding thick with  $CiSO_3H$  in glacial AcOH as described by Tanaka *et al.*<sup>14</sup> The reported procedures proved to be readily reproduced.

Glycine, N-(N-L-7-glutamyl-S-Sulfe-L-cystinyl), Disedium Sait, Dihydrate (51) (Sedium Glutathionate).

Glutathione (6.4 mmol) was added to a reaction mixture of sodium sulfite (26.0 mmol) in 98 mL of a 0.05 M CuSO<sub>4</sub> solution adjusted to pH 10 with concentrated ammonia. The reaction was stirred for 2  $\mu$ r at room temperature and then the mixture was kept in the refrigerator overnight. The solution (-40 mL) was

concentrated on a rotary evaporator and passed through a column of Dowex 50 W (H<sup>+</sup> form, 100-200 mesh; 2 x 20 cm) with water as eluant. The eluate containing GSSO<sub>3</sub>H was again concentrated, treated with 8.0 g of barium acetate, and dissolved in 25 mL of water. The resulting precipitate was removed by contrifugation and the barium salt of GSSO<sub>3</sub>H was precipitated from the supernatant by the addition of 5 volumes of 95% ethanol. The barium salt was reprecipitated 4 times with ethanol and was then dried over  $P_3O_5$  under vacuum. Yield 62%. Anal. calcd for  $C_{19}H_{18}N_5O_9S_3Ba-2H_3O$ : C, 21.49; H, 3.42; N, 7.51. Found: C, 21.51; H, 3.29; N, 7.02. Mass spec. (M + H)<sup>+</sup> 524, (M - H)<sup>-</sup> 522.

### Preparation of Sodium Giutathionate.

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Barium glutathionate (2.50 g) was dissolved in 20 mL of water and sodium sulfate (0.634 g) was added at room temperature Barium sulfate was removed by filtration and the filtrate freeze dried and stored in the freezer. (Yield 100%.) Anal. calcd for  $C_{10}H_{15}N_{2}O_{9}S_{2}\cdot 2H_{2}O$ : C, 25.69; H, 4.09; N, 8.99. Found: C, 25.58; H, 3.77; N, 8.88. Mass spec (M - H)<sup>+</sup> 430, (M + H)<sup>+</sup> 432, (M - Na) 408.

Synthesis of a-Amidinium thiosulfate S (Bante Salts) (52-56).

#### (a) a-Chioropropionitrile Hydrochiorides.

a-Chloropropionitrile (0.1 m) was added dropwise to a stirred solution of 0.01 m of sodium methoxide in dry methanol (100 mL) at 25 °C. After one hour of stirring, the amine hydrochlorides (0.11 m) were added and the reaction mixture was stirred for 16-24 h at 25 °C. The mixture was filtered to remove all solids and the solvent was removed from the filtrate. The resulting residue was triturated with other and the solid products were carried further without purification.

#### (b) a-Amidialumthiosulfates.

These were prepared for the corresponding a-chloroamidine hydrochlorides. a-Chloroamidine, dissolved in 25-30 mL of water, was treated with sodium thiosulfate and refluxed 1 hr. The reaction mixture was allowed to cool to room temperature, after which the compounds separated and were removed by filtration. Purification by recrystallization from ethanol (3 times) was followed by drying under reduced pressure.

#### Preparation of Dithiolethione 57.

(a) 0.005 Mole of ethyl benzoylacetate, 0.012 mole of Lawesson's reagent, and 0.01 mole of elemental sulfur in 10 mL hydrous toluene were kept at 110 °C for 10 hrs. After cooling to room temperature the mixture was placed on a silica gel column and the toluene was eluted with petroleum ether/ether (95/5).

The elucat was changed to petroleum ether/ether (70/30) and the 1,2-dithiole-3-thione was isolated.<sup>1</sup> MS and CHN analyses confirmed the structure. Yields were low in each atlangt.

(b) 0.1 Mole of cumane, 0.15 mole of sulfur, and 0.04 g of disclyiguanidine were refluxed for 21

hrs. The mixture was then kept at 5 °C for 2 hrs. to allow the 1,2-dithiole-3-thiose to crystallize.<sup>2</sup>

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TABLE 4. DISULFIDES AND RELATED COMPOUNDS. Elemental Analyses Calcd ۲

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Structure No.	Yield, %	Yield, % M.p., °C		%C	Found	<b>%</b> N	
24	45	192-194	C <sub>6</sub> H <sub>8</sub> N <sub>3</sub> O <sub>3</sub> S <sub>2</sub> (192.25)	31.25 31.28	4.17 4.17	14.58 14,44	
25	40	175-183	C <sub>6</sub> H <sub>7</sub> NO <sub>2</sub> S <sub>2</sub> ·H <sub>2</sub> O (183-23)	26.23 26.13	4.92 4.90	7.65 7.51	

TABLE 5. THIOSULFONATES.								
Structure No.	Yield, %	M.p., *C	Molecular Formula (Formula Wt.)	E. %C	lements Ca Fou %H	i Analy: icd und %N	945	Mass (FAB) cation, saion or MH <sup>+</sup>
26	74	256-260	CH <sub>3</sub> C <sub>3</sub> S <sub>2</sub> Na-H <sub>2</sub> O (152.16)	7.89 7.78	3.31 3.27			23, 111
27	66	280-281	C3H6O3S2Na (148.18)	16.21 16.03	3.40 3.58			23, 125
28	52	310-315	C <sub>3</sub> H <sub>7</sub> O <sub>3</sub> S <sub>3</sub> Na (162.20)	22.21 22.31	4.35 4.30			23, 139
29	55	285-286	C <sub>a</sub> H <sub>s</sub> O <sub>2</sub> S <sub>2</sub> Na (196.22)	36.73 36.26	2.57 2.55			23, 173
30	86	298-300	C7H7O353Na (210.25)	39.99 39.45	3.35 3.34			23, 187
31	69	>350	C <sub>e</sub> H <sub>e</sub> BrO <sub>2</sub> S <sub>2</sub> Na (275.14)	26.19 25.94	1.46 1.52			23, 251
32	78	325-330	C <sub>10</sub> H <sub>13</sub> O <sub>7</sub> S <sub>2</sub> Na (252.33)	47.60 47.49	5.19 5.18		25.41 25.41	2M - Na, 449 2M + Na, 495
33	60	314-316	C <sub>10</sub> H <sub>7</sub> O <sub>7</sub> S <sub>2</sub> Na (246.25)	48.76 48.71	2.86 2.76			23, 223
34	77	>300	C <sub>12</sub> H <sub>6</sub> S <sub>4</sub> O <sub>4</sub> Ne <sub>2</sub>	36.93 36.64	2.07 2.03			390-Na, 367 390-2Na, 345
35	26	236-238	C <sub>13</sub> H <sub>13</sub> NO <sub>3</sub> S <sub>3</sub> Na	44.81 49.15	4.18 4.16	4.84 4.73		M + H, 290

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TABLE 6. THROSULFATES.								
Structure No.	Yield, %	M.p., *C	Molecular Formula (Formula Wt.)	Elemental Analyses Calcd Found %C %H %N				
36	42	260-265	C1H4O854N82 (298.28)	<b>8.05 8.00</b> 1.34 1.31				
37	64	310-315	C3H4O854N83-H3O (330.32)	10.91 2.44 10.98 2.39				
38	52	280-284	CaH14OassNag-H2O (374.42)	19.36 3.78 18.95 3.58				
39	68	245-250	C <sub>8</sub> H <sub>16</sub> O <sub>8</sub> S <sub>4</sub> Na <sub>2</sub> -H <sub>2</sub> O (400.45)	24.00 4.53 24.13 4.59				
40	70	172-175	C <sub>18</sub> H <sub>20</sub> O <sub>9</sub> S <sub>4</sub> Na <sub>2</sub> •H <sub>2</sub> O (428.51)	<b>28.03 28.33</b> 5.17 5.18				
41	57	101-102	C <sub>4</sub> H <sub>11</sub> O <sub>5</sub> S <sub>5</sub> Na-H <sub>3</sub> O (268.29)	26.86 4.88 26.19 4.33				
42	36	140-150	C <sub>8</sub> H <sub>15</sub> O <sub>8</sub> S <sub>2</sub> Na-H <sub>2</sub> O (296_34)	32.43 5.78 32.46 5.38				
43	62	138-140	C <sub>3</sub> H <sub>4</sub> Na <sub>2</sub> S <sub>4</sub> O <sub>7</sub> +H <sub>2</sub> O (344.33)	10.46 1.75 10.34 1. <del>59</del>				
44	30	195-198	C <sub>8</sub> H <sub>8</sub> Na <sub>2</sub> S <sub>4</sub> O <sub>6</sub> -1.5H <sub>2</sub> O (317.42)	23.94 2.76 24.05 2.63				
45	87	194-196 (lit. mp 195-196)	C3H7NO3S3 (157.22)	15.28 4.49 8.91 15.23 4.40 8.75				
46	42	160-162	C <sub>4</sub> H <sub>11</sub> S <sub>2</sub> NO <sub>3</sub> (185.26)	24.96         6.17         7.27           25.00         6.17         7.03				
47	60	184-186 (lit. mp 189-196)	C <sub>3</sub> H <sub>9</sub> NO <sub>3</sub> S <sub>3</sub> (171.25)	21.04         5.30         8.18           21.07         5.33         7.82				
48	90	204-205 (lit. mp 204-205)	C <sub>2</sub> H <sub>7</sub> NO <sub>5</sub> S <sub>2</sub> ·H <sub>2</sub> O (219.22)	16.43 4.13 6.39 16.73 4.33 6.16				
49	71	202-203 (lit. mp 202-203)	C <sub>g</sub> H <sub>11</sub> NO <sub>g</sub> S <sub>3</sub> (229.28)	26.20 4.84 6.10 26.19 4.84 5.98				
50	90	214-216 (lit. mp 254-255)	C <sub>e</sub> H <sub>7</sub> NO <sub>5</sub> S <sub>2</sub> (205.26)	35.10         3.43         6.82           35.18         3.45         6.66				
51	62		C <sub>18</sub> H <sub>18</sub> Na <sub>9</sub> S <sub>3</sub> N <sub>3</sub> O <sub>8</sub> -2H <sub>3</sub> O (449.38)	25.69 4.09 8.99 25.58 3.77 8.88				
52	48	154-156	C <sub>9</sub> H <sub>8</sub> N <sub>2</sub> O <sub>5</sub> S <sub>2</sub> (185.25)	19.56 4.38 15.21 19.51 4.33 15.02				
53	74	174-175 (174)	C <sub>4</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub> (198.27)	24.23         5.08         14.13           24.33         5.02         14.03				

# TABLE 6. (Continued)

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Structure No.	% Yield	M.p., *C	Molecular Formula (Formula Wt.)	Elema	Elemental A. Caiod Found NC 94H	
54	89	144-145 (164)	C <sub>4</sub> H <sub>10</sub> N <sub>2</sub> O <sub>2</sub> S <sub>2</sub> (198.27)	24.23 24.30	5.08 5.14	14.13 14.03
55	36	154-156 149-150	C <sub>6</sub> H <sub>12</sub> N <sub>2</sub> O <sub>3</sub> S <sub>3</sub> ·H <sub>2</sub> O (244.30)	28.29 28.27	5.70 5.75	13.19 13.08
56	78	154-156	C <sub>9</sub> H <sub>13</sub> N <sub>3</sub> O <sub>3</sub> S <sub>3</sub> (260.34)	41.52 41.69	4.65 5.04	10.76 10.22

	TABLE 7.	3- <i>H</i> -1,2-DITHIO	LE-3-THIONES.		
Structure No.	% Yield	M.p., *C	Moiocular Formula (Formula Wt.)	Elementa Ca Fo %C	l Analyses licd und %H
57	71	118-121	C <sub>9</sub> H <sub>6</sub> S <sub>3</sub> (210.33)	51.43 51.64	2.86 2.86

VI. SUMMARY

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TABL	TABLE 8. COMPOUNDS SUBMITTED FOR TESTING AS ANTICYANIDE AGENTS. CONTRACT NO. DAMD17-99-C-00111 9 MARCH 1991 - 17 MARCH 1992 (STRUCTURES SHOWN IN TABLE 10)				
WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No., (pages)	
002712AD	BM 11001	7838	F850-141-2	5, (13)	
002712AE	BM 09565	7838	F850-141-2	5, (13)	
271154AA	BM 09574	7839	F850-151-2	7, (3-5)	
271155AA	BM 0	7845	G076-39-1	5, (6-8)	
271156AA	BM 09592	7846	G076-43-1	5, (6-8)	
271157AA	BM 09609	7847	G076-40-1	5, (6-8)	
271158AA	BM 09618	7848	G076-47-1	5, (6-8)	
271142AA	BM 09350	7849	G07E-37-2	5, (6-8)	
002250AB	BM 09369	7864	G0164-27-1	5, (12-13)	
002250AC	BM 11010	7864	G0164-27-1	5, (12-13)	
000156AD	BM 09378	7865	G076-54-1	5, (17-13)	
271143AA	BM 09387	7866	G076-58-2	5, (12-13)	
025102AU	BM 09396	7867	G076-55-2	5, (12-13)	
000585AF	BM 09403	7868	G076-53-1	5, (12-13)	
271144AA	BM 09412	7869	G076-59-1	5, (12-13)	
000363AD	BM 09421	7870	G076-52-1	5, (12-13)	
037733AC	BM 09430	7871	G076-56-1	5, (12-13)	
271145AA	BM 09449	7872	G076-57-2	5, (12-13)	
000361AW	BM 09458	7873	G076-51-1	7, (3-5)	
271146AA	BM 09467	7908	G076-61-1	5, (9-11)	
271147AA	BM 09476	7909	G076-74-1	5, (9-11)	
271148AA	BM 09485	7910	G076-71-1	5, (9-11)	
271149AA	BM 09494	7911	G076-75-1	5, (9-11)	
000125AC	BM 501	7913	G076-64-1	5, (9-11)	
271150AA	BM 09510	7914	G076-62-1	5, (9-11)	
271151AA	BM 09529	7915	G076-70-1	5, (9-11)	
002852AC	BM 09538	7916	G076-78-1	5, (9-11)	
271152AA	BM 09547	7917	G076-77-1	\$, (9-11)	



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WR No.	WR Bottle No.	SoRI No.	Sample No.	Description in Quarterly Progress Report No, (pages)
271153AA	BM 09556	7918	G076-72-1	5, (9-11)
001758AB	BM 10317	7928	G076-86-1	6, (7-9)
001757AC	BM 10326	7929	G076-89-1	6, (7-9)
272681AA	BM 10335	7530	G076-81-1	6, (7-9)
102233AB	BM 10344	7931	G076-82-1	6, (7-9)
001868AC	BM 10353	7932	G076-87-1	6, (7-9)
276495AA	BM 11029	7934	G076-107-1	6, (8)
276496AA	BM 11038	7984	G164-121-1	7, (3-5)
276497AA	BM 11047	7 <b>985</b>	G164-127-1	7, (3-5)
276498AA	BM 11056	7 <b>98</b> 6	G0395-07-1	7, (3-5)
276499AA	BM 11065	7 <b>987</b>	G0395-19-1	7, (3-5)
000362AB	BM 11074	8112	G076-103-1	6, (7-9)
276500	BM 11083	8113	G076-105-1	6, (7-9)
276501AA	BM 11092	8114	G076-109-1	6, (7-9)
002708AC	BM 11109	8115	G076-95-1	6, (7-9)
001756AB	BM 11118	8116	G076-93-1	6, (7-9)
•		8140	G395-49-1	8, (5-8)
•		8141	G395-75-1	<b>£</b> , (5-8)
•		8158	G395-85-1	8, (5~8)
•		8168	G395-87-1	\$, (5-8)
•		\$170	G454-15-1	8, (11-12)
٠		8171	G076-129-1	8, (11-12)
•		8172	G454-03-03	7, (6-8)
•		\$175	G395-97-1	8, (5-8)
٠		8177	G395-99-2	\$, (5-8)
•		8178	G395-101-2	8, (5-8)
•		8179	G395-105-2	\$, (5-\$)
•		\$180	G395-109-3	8, (5-8)
•		\$184	G395-107-4	8, (10)
•		\$190	G454-37-1	8, (11-12)
٠		8191	G454-39-1	8, (11-12)

WR and bottle numbers unavailable; will be included in subsequent report.

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	9 MARCH 1991 - 17 MARCH 1992		
ICD No.	WR No.	WR Bottle No.	SoRI No.
1761	268785	BM 05503	7602
1819	268834	BM 06073	7669
1826	268841	BM 06144	7675
1830	268820	BM 06153	7676
1831	257838	BM 06162	7677
1827	268844	BM 06171	7678
1832	268798	BM 06180	7679
1829	268846	BM 06206	7685
1898	268911	BM 07141	7703
1899	268912	BM 07150	7704
1900	268913	BM 07169	7705
1901	268914	BM 07178	7720
1902	268915	BM 07187	7721
1903	268916	BM 07196	7722
1904	268917	BM 07203	7723
1905	268918	BM 07212	7724
1906	268919	BM 07221	7725
1907	268920	BM 07230	7726*
1908	268921	BM 07249	7727
1909	268922	BM 07258	7728
1910	268923	BM 07267	7730
1911	268924	BM 07276	7731
2008	090892	BM 08317	7730
2009	269153AA	BM 08326	7800
2012	269156AA	BM 08353	7803
2013	269157AA	BM 08362	7804
2014	269158AA	BM 04371	7805
2015	269159AA	EM 08380	7806
2016	269160+	BM 08399	7807
2019	269163AA	BM 04424	7810

TABLE 9. CANDIDATE COMPOUNDS TESTED FOR ANTICYANIDE REFFICACY DURING THIS REPORT PERIOD 9 MARCH 1991 - 17 MARCH 1992

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ICD No.	WR No.	WR Bottle No.	SoRI No.
2022	269166AA	BM 08451	7813
2115	002712AE	BM 09565	7838
2160	271154AA	BM 09574	7839
2117	271156AA	BM 09592	7846
2118	271157AA	BM 09609	7847
2119	271158AA	BM 096180	7848
2095	000156AD	BM 09378	7865
2096	25102AV	BM 09396	7867
2097	000585AF	BM 09403	7868
2098	271144AA	BM 09912	7869
2099	000363AD	BM 09421	7870*
2100	037733AC	BM 09430	7871
2102	000361AW	BM 09458	7873
2104	271147AA	BM 09476	7909
2107	271148AA	BM 09485	7910
2108	271149AA	BM 09494	7911
2113	271152AA	BM 09547	7917
2114	271153AA	BM 09556	7918
2188	001758AB	BM 10317	7928



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Other identifying numbers (WR No., WR "bittle No., Our Sample No.) are listed along with SoRi number in Table 6. Structures are shown in order of increasing SoRi numbers.



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VII. REFERENCES

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